REMARKS/ARGUMENTS

After entry of the amendments, Claims 1, 5, 6, and 35-50 remain pending in this application. Claims 7, 31-34, and 51-52 have been previously withdrawn. Claims 2-4 and 8-30 have been cancelled previously. Claims 1, 38, 46, and 49 have been amended.

Claim 1 was amended in response to Examiner's rejection under 35 U.S.C. 112, second paragraph, as described further below. This amendment is fully supported by page 2, lines 12-14, and page 3, lines 8-10 of the parent application as originally filed.

Claims 38 and 46 were amended in response to Examiner's rejection under 35 U.S.C. 112, second paragraph, as described further below. These amendments are fully supported by page 4, lines 7-9 of the parent application as originally filed.

Claim 49 was amended in response to Examiner's objection to the improper format of the sequence identifier, as described in paragraph 9 of the present Office Action.

The specification has also been amended to overcome the Examiner's objections. The title has been amended in response to the Examiner's objection that the prior title was not descriptive, as detailed in paragraph 5 of the present Office Action. Applicants believe the new title is descriptive of the invention as claimed. This amendment is fully supported by the entire document, in particular page 3, lines 17-29, and page 4, lines 1-26 of the parent application as originally filed. The abstract has been amended to remove legal phraseology in response to the Examiner's objection, as stated in paragraph 6 of the present Office Action. This amendment is fully supported by the entire document, in particular page 3, lines 8-10 and 17-29, and page 4, lines 1-26 of the parent application as originally filed. The specification has been further amended to identify the proprietary nature of certain trademarks used in the application, in response to the Examiner's objection, as detailed in paragraph 8 of the present Office Action.

Entry of these amendments is respectfully requested.

Claim Rejections – 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 1, 38, and 46 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention under 35 U.S.C. § 112, second paragraph.

In paragraph 11A of the present Office Action, the Examiner states that "Claim 1 is indefinite in the recitation of 'co-stimulatory signal 2,' because the metes and bounds of the claimed invention are unclear." The Examiner notes that "other molecular interactions are also known in the art to mediate secondary costimulatory signals ... [t]herefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention." The Examiner cites examples of such molecular interactions, including ICOS with ICOS-L and PD01 with PD-L1 and PD-2. As amended, Claim 1 is specifically directed to modulation of B7/CD28 interactions, thereby particularly pointing out and distinctly claiming the subject matter which Applicants regard as the invention in compliance with 35 U.S.C. § 112, second paragraph.

In paragraph 11B of the present Office Action, the Examiner also finds that claims 38 and 46 are indefinite in the recitation of 'wherein the immunoglobulin gamma is human Cγ1,' finding that 'Cγ1' lacks proper antecedent basis in the recitation of 'immunoglobulin.'" More specifically, the Examiner notes that the designation Cγ1 apparently refers to the constant region of the heavy chain of the γ1 subtype of IgG, such that "the recitation reads as 'immunoglobulin is a part of an immunoglobulin,' and as such, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention." As amended, Claims 38 and 46 provide proper antecedent basis for human Cγ1 by reciting the constant region with the claim and providing that it is of the human Cγ1 subtype.

As amended, Applicants believe that Claims 1, 38 and 46 particularly point out and distinctly claim the subject matter which Applicants regard as the invention in compliance with 35 U.S.C. § 112, second paragraph. Accordingly, Applicants respectfully request the Examiner withdraw the 35 U.S.C. § 112, second paragraph rejections of Claims 1, 38, and 46.

Claim Rejections – 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claim 1 as non-enabled under 35 U.S.C. § 112, first paragraph. As described in paragraph 13 of the present Office Action, the Examiner finds that "the specification, while being enabling for a biological reagent comprising porcine CTLA-4 that inhibits rejection of a xenotransplanted organ in pigs, does not reasonably provide enablement for a generically recited biological reagent comprising porcine CTLA-4 that inhibits rejection of a xenotransplanted organ." Examiner further states in paragraph 13 of the present Office Action

that "it is highly unpredictable whether the porcine CTLA4 would be effective when administered to species other than pig."

Applicants respectfully submit that the present invention is directed to xenospecific immunosuppression, not systemic immunosuppression. Xenospecific immunosuppression is possible because porcine CTLA-4 differentially and preferentially binds to pig B7 – not human B7. That differential binding is at the heart of the present invention. The species-specific binding of porcine CLTA-4 to pig B7 permits porcine CTLA-4 to be effective in cross-species, i.e., to inhibit rejection of xenotransplanted organs.

Differential binding and the importance of xenograft-specific immunosuppression to the present invention are described in the specification. As stated on page 3, lines 21-29, and page 4, lines 1-3 of the parent application as originally filed:

> *Although CTLA-4 from one organism (e.g. Pig) is able to bind to B7 from another organism (e.g. Human), the highest avidity is found for allogeneic B7. Whilst soluble CTLA-4 from the donor organism can thus bind to both recipient B7 (on normal cells) and donor B7 (on xenotransplanted cells),* ***it preferentially binds B7 on the xenograft. This results in xenograft-specific immunosuppression, unlike the administration of CTLA-4 from the recipient organism, which would tend to lead to systemic immunosuppression****. By blocking the interaction between B7 on the xenogeneic donor cells and CD28 on recipient T-cells, co-stimulatory signal 2 is not delivered to the T-cell of the recipient. Xenoreactive T-cells are therefore rendered anergic. (emphasis added).*
>
> *The invention thus provides a method of inducing xenotransplant tolerance in an organ recipient, comprising the administration to said recipient of a soluble form of the CTLA-4 protein from the xenogeneic donor organism.*

As another example, page 13, lines 24-27 of the parent application as originally filed:

> *As illustrated in figure 5, human and porcine CTLA4-Ig appeared to have similar binding characteristics on human cells expressing porcine B7. Unlike human CTLA4-Ig, however, [porcine] CTLA4-Ig failed to bind human B7, implying that [porcine]* ***CTLA4-Ig binds preferentially to porcine B7 and is useful as a species-specific reagent****. (emphasis added).*

The ability of porcine CTLA-4 to promote xenograft-specific immunosuppression was described in a peer-reviewed study published in 2000. Vaughn et al., Journal of Immunology (2000) 165: 3175-3181. Vaughn et al. describes the need for a reagent that would be "graft-

specific, targeting only those interactions with the transplanted tissue." p. 3180. Vaughn et al. then provides *in vitro* data that supports a "significant degree of species specificity" in the action of porcine CTLA-4-Ig and identifies it as "a potentially important therapeutic reagent for use in clinical xenotransplantation." p. 3175.

While not specifically relied upon in support of enablement, the Applicants wish to note that a later *in vivo* study by the inventors, using a xenograft model, provided further support for the use of porcine CTLA-4 in xenospecific immunosuppression. Mirenda et al., Diabetes (2005) 54: 1048-1055. In this study, porcine CTLA4-Ig was used to inhibit direct T-cell xenoresponses after porcine islet xenografting in STZ-induced diabetic mice. "Injection of [porcine] CTLA4-Ig led to substantial prolongation of islet graft survival ... whereas [murine] CTLA4-Ig had only a minimal effect." p. 1052. In normal mice receiving porcine islets, porcine CTLA-4 was shown to preferentially bind porcine B7 and was effective at inhibiting the direct mouse anti-pig T-cell response. This, in combination with murine CTLA4-Ig given at a later time post-transplant to act on the indirect T-cell response, lead to permanent survival of porcine islet grafts. See p. 1053. These results demonstrate that administration of porcine CTLA-4 "could have clinical utility in porcine islet xenotransplantation." p. 1048.

Accordingly, the Applicants maintain that the present invention is enabled with respect to the use of porcine CTLA-4 to promote xenograft-specific immunosuppression and inhibit the rejection of xenotransplanted organs. Thus, the Applicants respectfully request the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection of Claim 1.

Claim Rejections – 35 U.S.C. § 102(e)

The Examiner has rejected Claims 1, 5, 6, 35-38, 41-46, and 50 under 35 U.S.C. § 102(e) as anticipated by the Larsen patent. The Applicants respectfully submit that the Larsen patent does not teach or suggest each and every recitation of independent Claims 1, 5, and 41. Specifically, the Larsen patent fails to teach or suggest the use of porcine CTLA-4 to promote xenograft-specific inhibition of T-cell mediated rejection of a xenotransplanted organ. Rather, the Larsen patent is directed to systemic immunosuppression (not xenograft-specific inhibition as

in the present invention) using endogenous molecules from the recipient to inhibit the rejection of transplanted tissues.

The Larsen patent specifically teaches methods comprising "an **endogenous** molecule (e.g., antigen) on a cell selected from the group consisting of gp39 and CD40 from binding its **endogenous** ligand and preventing an **endogenous** molecule on a cell selected from the group consisting of CTLA4, CD28, and B7 from binding its **endogenous** ligand (emphasis added)." (Citing the Larsen patent Col. 2, lines 61-67, and Col. 3, line 1). The Larsen patent, therefore, uses CTLA-4 from the **same species** as the host (e.g., human CTLA-4 into human recipient) whereas the present invention uses CTLA-4 from a **different (or cross) species** (e.g., porcine CTLA-4 into human recipient). Nor does Larsen teach or suggest that porcine CTLA-4 could not be used in a cross-species host (e.g., porcine CTLA-4 into human recipient).

Because the Larsen patent teaches and suggests the use of endogenous (i.e., recipient) CTLA-4 and the present invention uses CTLA-4 from the xenogeneic donor (i.e., porcine), the CTLA-4 amino acid sequences are not inherently the same as the Examiner suggests. In fact, the present invention establishes that the differences in the amino acid sequences between porcine CTLA-4 and human CTLA-4 "is believed to be of key importance to the advantageous differential binding of [porcine CTLA-4] to human and pig B7." See page 12, lines 25-29, and page 13, lines 1-2.

Accordingly, since the Larsen patent does not teach or suggest each and every recitation of independent Claim 1, 5 or 41, the Applicants respectfully request the Examiner withdraw the 35 U.S.C. §102(e) rejection of these claims.

Claim Rejections – 35 U.S.C. § 103(a)

The Examiner has rejected Claims 5, 35, 39, 41, 43, and 47 under 35 U.S.C. § 103(a) as obvious over the Larsen patent in view of U.S. Patent No. 6,165,476 to Strom et al. (hereinafter "the Strom patent"). The Examiner stated in paragraph 17 of the present Office Action that "Larsen et al. ... teach fusion polypeptides comprising porcine CTLA-4 and immunoglobulin ... [and] Strom et al. teach that connecting members in a fusion protein by a flexible linker can increase biological activity ... ." The Applicants respectfully submit that the combination of the Larsen patent and the Strom patent is not the claimed invention.

As stated above in the context of anticipation, the Larsen patent is directed to systemic immunosuppression using endogenous molecules from the recipient to inhibit the rejection of transplanted tissues from the same species as the host (e.g., human CTLA-4 into human recipient). The present invention, on the other hand, uses CTLA-4 from a different species than the host (e.g., porcine CTLA-4 into human recipient) to achieve xenograft-specific inhibition. These are two separate and distinct approaches to prevent rejection of xenotransplanted organs. As such, the combination of the Larsen patent and the Strom patent does not provide the claimed invention.

Accordingly, the Applicants respectfully request the Examiner withdraw the 35 U.S.C. §103(a) rejection of Claims 5, 35, 39, 41, 43 and 47.

Claim of Priority and Other

In paragraph 4 of the present Office Action, the Examiner has acknowledged the Applicants' timely claim for foreign priority based on an application filed in the United Kingdom on April 30, 1998 (the "United Kingdom application"). The Examiner notes, however, that the Applicants have not filed a certified copy of the United Kingdom Application as required by 35 U.S.C. 119(b). Applicants assert that they have complied with 35 U.S.C. 119(b), 37 CFR 1.55(a)(2), MPEP 1893.03(c), and PCT Rule 17(a)-(b) and may properly claim the benefit of foreign priority based on an application filed in the United Kingdom on April 30, 1998. A certified copy of the United Kingdom application will be provided under separate cover.

The Examiner objected to Claims 40, 48, and 49 as being dependent upon a rejected base claim in paragraph 18 of the present Office Action, but further stated that these Claims would be allowable if rewritten in independent form. Applicants believe that the previously rejected base Claims are in condition for allowance upon entry of these remarks and amendments. Accordingly, Applicants believe that dependent Claims 40, 48, and 49 are also in condition for allowance upon entry of these remarks and amendments.

Applicants are aware of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a), as noted by the Examiner in paragraph 16 of the present Office Action.

CONCLUSION

The foregoing is submitted as a full and complete response to the Office Action mailed on December 8, 2005. The Applicants and the undersigned thank Examiner Ouspenski for considering these remarks and amendments. The Applicants respectfully submit that the present application is in condition for allowance. Such action is hereby courteously solicited.

No fees are believed to be due in connection with this Response to Non-Final Office Action. The Commissioner is hereby authorized to charge any underpayment of fees to Deposit Account No. 11-0980.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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